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Introductory Remarks: The Testes

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This Target Organ Symposium is the 10th in a continuing series. Only one previous Target Organ Symposium, that on the gonads, dealt with the endocrine system. The Organizing Committee for the Endocrine Target Organ Symposium fully recognizes the diversity of scientific topics to be included into this two-day period. Nevertheless, it seemed just as defensible to include these diverse topics into one symposium as to attempt to splinter such topics in the context of toxicology. The format of the endocrine symposium is to devote separate sessions to the testes, the ovaries, the adrenal cortex, and to the thyroid gland. More specifically, each session provides an overview or state-of-the-art approach to discussing pituitary and target organ relationships. Some presentations deal with the biochemical actions of the particular target organ hormone, and finally some factors, including chemicals and environmental, that may affect these endocrine systems are discussed.

This initial session focuses upon the physiology and biochemistry of the testes and those factors that affect gonadal function. To set the tone of the symposium, particularly as it relates to occupational and environmental factors and the male reproductive system, it might be of interest to recall a few recent occurrences that have received widespread attention in the popular press and newspapers. In 1977, the Metatocide, dibromochloropropane (DBCP), was reported to cause azoospermia or oligopsermia in men working in a California pesticide factory. The mechanism of DBCP toxicity is unknown, but it may act like an alkylating agent upon germinal epithelium.

A somewhat more controversial example of chemicals contaminating the environment and adversely affecting the reproductive system is Agent Orange. Agent Orange, a herbicide, was used extensively in Vietnam to defoliate the jungle. Agent Orange is a phenoxy herbicide known as 2,4,5-T or 2,4,5-trichlorophenoxyacetic acid. There is a contaminating chemical in 2,4,5-T preparations called dioxin, also known as TCDD. TCDD is an inseparable, through unwanted contaminant of 2,4,5-T. There is some evidence, albeit not conclusive, that 2,4,5-T is a teratogen, a mutagen, and may cause impotency. Animal studies have shown that 2,4,5-T, in large doses, can adversely affect steroid metabolism (Table 1). It may be seen that varying doses of 2,4,5-T inhibit not only steroid metabolism, but also the assimilation of total tritiated testosterone by androgen-dependent organs such as the prostate.

DDT is also found in the environment and can also be assimilated by male reproductive organs. Table 2 reveals the assimilation of tritiated DDT or its radiometabolites by the testes and by other male reproductive organs of experimental animals. The prostate has a considerable avidity for labeled DDT. Note also that radioactivity is also present in the seminal plasma. Varying doses of DDT can also affect the uptake of tritiated testosterone by the mouse prostate gland (Table 3). It may be seen that this chlorinated hydrocarbon interferes with the assimilation of androgen in male accessory sex organs.

Still other xenobiotics can be detected in the male reproductive tract and the testes. For example, a single oral administration of carbaryl-^{14}C results in the distribution of this pesticide and its radiometabolites in several organs of the male reproductive system (Table 4). Carbaryl or its radiometabolites can be detected in several reproductive organs in at least three different species. The testes of the rat, mouse, and the dog have been shown to contain amounts of carbaryl. Several studies from the Soviet Union have also described carbaryl-induced changes in testicular function in experimental animals. However, in humans, a cohort of over 100 male carbaryl production workers in a U.S. factory failed to reveal any significant changes in sperm counts or any infertility.

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Table 1. Chromatographic identification of radioactive steroid in mouse anterior prostate glands following ten-day oral administration of 2,4,5,-T[a]

Daily dose, mg/kg[b]	Androstanediol		Testosterone		Dihydrotestosterone		Androstenedione		Reduction in total radioactivity, %
	% Total	% Change	% Total	%Change	%Total	%Change	%Total	%Change	
Control	15	—	44	—	30	—	11	—	—
6.25	15	–4	44	–13	28	–23	13	1	14
12.5	15	–19	42	–22	28	–24	13	–4	19
25.0	15	–37	40	–40	31	–33	14	–14	35

[a] Data of Lloyd et al. (*1*).
[b] Mice were killed 5 min after injection (intraperitoneal) of testosterone-1, 2-$^3H_2$. Mean of at least six pooled prostatic homogenates from six or more lobes.

Table 2. Distribution of radioactivity in various organs of the anesthetized dog 30 min after a single intravenous injection of [^{3}H] DDT.[a]

Organ[b]	Radioactivity, cpm/mg wet weight
Testes	2[c]
Prostate	5
Vas deferens	3
Adrenal	31
Liver	34
Kidney	12
Muscle (diaphragm)	3

[a] Data of Thomas (*2*).
[b] Dose level of [^{3}H] DDT was 0.18 μCi/kg body weight.
[c] Average of at least three dogs.

Table 3. Effect of DDT on the 5 min uptake of radioactivity from testosterone-1, 2-^{3}H by the anterior prostate gland of intact mice.[a]

Dose (PO), mg/kg	Radioactivity, dpm/mg
Control[b]	310 ± 15
12.5	210 ± 15[c]
25	173 ± 14[c]
50	124 ± 13[c]

[a] Data of Smith et al. (*3*).
[b] Mean ± SEM of at least 12 organs.
[c] All treated groups are significantly lower than controls $p < 0.05$.

Table 4. Distribution of radioactivity following a single dose of [^{14}C] carbaryl (24 μCi/kg equivalent to 0.9 mg/kg, PO) to normal mice.[a]

Organ	Radioactivity, cpm/mg wet weight at various times after administration				
	1 hr	2 hr	4 hr	24 hr	48 hr
Prostate[b]	6.6	5.6	5.5	4.2	2.7
Seminal vesicles	5.2	4.4	4.6	3.8	2.8
Testes	5.5	4.6	4.6	3.7	2.9
Seminal plasma	3.8	4.4	3.7	2.8	
Epididymal fat	4.3	4.2	3.9	4.0	2.5

[a] Data of Thomas et al. (*4*).
[b] Mean of three organs.

Despite examples of xenobiotics affecting the male reproductive system, little is known about their basic mechanism of adverse action. Only rather recently have interests began to focus upon basic mechanisms of target organ toxicity. It is hoped that discussions during this session on the testes and those on other target organs being considered during this Target Organ Symposium will elucidate and update some of these basic biochemical mechanisms in endocrine glands. Only with a full appreciation of the underlying physiological modulation of these organs will there be a better understanding of how various chemicals and/or drugs affect these systems. The subsequent presentations should serve to clarify selected aspects of testicular biochemistry and to what extent they are adversely affected by chemicals and environmental factors.

REFERENCES

1. Lloyd, J. W., Thomas, J. A., and Mawhinney, M. G. 2,4,5T and the metabolism of testosterone-1,2-$^3H_2$ by mouse prostate glands. Arch. Environ. Health, 26: 218 (1973).
2. Thomas, J. A. Effect of pesticides on the reproductive system. In: Advances in Sex Hormone Research, Vol. 1, University Park Press, 1975, p. 208.
3. Smith, M. T., Thomas, J. A., Smith, C. E., Mawhinney, M. G., and Lloyd, J. W. Effects of DDT on radioactive uptake from testosterone-1,2-^{3}H by mouse prostate glands. Toxicol. Appl. Pharmacol. 23: 159 (1972).
4. Thomas, J. A., Dieringer, C. S., and Schein, L. L. Effects of carbaryl on mouse organs of reproduction. Toxicol. Appl. Pharmacol. 28: 144 (1974).